PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 October 2000 (09.10.00)	
International application No. PCT/US00/04274	**Applicant's or agent's file reference** X-11920
International filing date (day/month/year) 18 February 2000 (18.02.00)	**Priority date** (day/month/year) 19 February 1999 (19.02.99)
Applicant DODGE, Jeffrey, Alan et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

01 September 2000 (01.09.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Maria Kirchner
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

William R. BOUDREAUX
ELI LILLY AND COMPANY
Lilly Corporate Center
++++++++++++++++++++++++++++++++++
Indianapolis, Indiana 46285
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	12.01.2001
Applicant's or agent's file reference: X-11920	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/04274	18/02/2000	19/02/1999

Applicant
ELI LILLY AND COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith th international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	DA ROCHA, O. Tel.+49 89 2399-8101

Form PCT/IPEA/416 (July 1992)

15

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
X-11920		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/04274	18/02/2000	19/02/1999
International Patent Classification (IPC) or national classification and IPC C07K5/062		
Applicant ELI LILLY AND COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01/09/2000	12.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer G. Willière Telephone No. +49 89 2399 8548

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/04274

I. Basis of the rep rt

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-221 as originally filed

Claims, No.:

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 4 and 5.

because:

☒ the said international application, or the said claims Nos. 4 and 5 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*): **see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-9
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

R It m III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 4 and 5 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: EP-A-0 662 481 (MERCK & CO INC) 12 July 1995 (1995-07-12)
   D2: EP-A-0 615 977 (MERCK & CO INC) 21 September 1994 (1994-09-21)
   D3: WO 98 16527 A (TANIGUCHI KIYOSHI ;KURODA SATORU (JP); SHIMIZU YASUYO (JP); FUJISA) 23 April 1998 (1998-04-23)
   D4: US-A-5 721 250 (MORRIELLO GREGORI J ET AL) 24 February 1998 (1998-02-24)

2. The present application relates to non-peptidyl growth hormone secretagogues (see claim 1, formula I) being metabolically more stable than the corresponding peptidyl compounds.

3. None of the growth hormone secretagogues disclosed in D1 to D4 are structurally close enough to the presently claimed compounds in order to be of particular relevance.

4. It may thus be concluded that the presently claimed subject-matter is novel and involves an inventive step in the light of the prior art as cited in the International Search Report (article 33(2) and (3) PCT).

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 99 08697	25.0.1999	19.08.1998	19.08.1997
WO 99 08699	25.02.1999	19.08.1998	19.08.1997

Re Item VII

Certain defects in the international application

1. The non-published United States Serial numbers should be replaced by the corresponding published patent numbers (see page 4, lines 7 to 9).

Re Item VIII

Certain observations on the international application

Dependent method claim 8 refers to claim 7 which is concerned with a pharmaceutical formulation rather then a method (article 6 PCT).

NIK

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
X-11920		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 04274	18/02/2000	19/02/1999
Applicant		
ELI LILLY AND COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/04274

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/062 A61K38/05 A61P19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 08697 A (LILLY CO ELI ;KAUFFMAN RAYMOND FRANCIS (US); PALKOWITZ ALAN DAVID) 25 February 1999 (1999-02-25) claims	1-9
P,X	WO 99 08699 A (BRYANT HENRY UHLMAN ;COPP JAMES DENSMORE (US); FAHEY KENNAN JOSEPH) 25 February 1999 (1999-02-25) claims	1-9
A	EP 0 662 481 A (MERCK & CO INC) 12 July 1995 (1995-07-12)	
A	EP 0 615 977 A (MERCK & CO INC) 21 September 1994 (1994-09-21)	

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2000	27/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cervigni, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/04274

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 16527 A (TANIGUCHI KIYOSHI ;KURODA SATORU (JP); SHIMIZU YASUYO (JP); FUJISA) 23 April 1998 (1998-04-23)	
A	US 5 721 250 A (MORRIELLO GREGORI J ET AL) 24 February 1998 (1998-02-24)	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/04274

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9908697 A	25-02-1999	AU 9471598 A	08-03-1999
		BR 9803168 A	11-01-2000
		EP 0898963 A	03-03-1999
WO 9908699 A	25-02-1999	AU 9025698 A	08-03-1999
		EP 0933365 A	04-08-1999
		NO 20000823 A	12-04-2000
EP 0662481 A	12-07-1995	US 5578593 A	26-11-1996
		AT 178070 T	15-04-1999
		AU 673017 B	24-10-1996
		AU 5232193 A	23-06-1994
		CA 2110672 A	12-06-1994
		CN 1092767 A,B	28-09-1994
		DE 69324148 D	29-04-1999
		DE 69324148 T	28-10-1999
		ES 2129072 T	01-06-1999
		HR 931484 A	30-04-1996
		IL 107836 A	04-01-1998
		JP 2509147 B	19-06-1996
		JP 7097367 A	11-04-1995
		MX 9307851 A	30-06-1994
		SI 9300647 A	30-09-1994
		AU 673552 B	14-11-1996
		AU 5232093 A	23-06-1994
		BG 61979 B	30-11-1998
		BG 99710 A	31-01-1996
		BR 1100850 A	07-12-1999
		CA 2110670 A	12-06-1994
		CN 1092071 A,B	14-09-1994
		CZ 9501514 A	13-12-1995
		CZ 9501515 A	13-12-1995
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		FI 952862 A	09-06-1995
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		HU 9500324 A	28-09-1995
		HU 73228 A	29-07-1996
		HU 72076 A	28-03-1996
		JP 2509530 B	19-06-1996
		JP 6263737 A	20-09-1994
		KR 203962 B	15-06-1999
		MX 9307850 A	30-06-1994
		NO 952294 A	10-08-1995
		NO 952295 A	10-08-1995
		NZ 258412 A	29-01-1997
		NZ 258429 A	26-05-1997
		PL 309331 A	02-10-1995
		PL 309332 A	02-10-1995
		SI 9300646 A	30-09-1994
		SK 75995 A	08-11-1995
		WO 9413696 A	23-06-1994
		WO 9419367 A	01-09-1994
		US 5536716 A	16-07-1996
		US 5652235 A	29-07-1997
		ZA 9309272 A	08-08-1994
		ZA 9309274 A	08-08-1994
EP 0615977 A	21-09-1994	US 5536716 A	16-07-1996

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0615977 A		AU 673552 B	14-11-1996
		AU 5232093 A	23-06-1994
		BG 61979 B	30-11-1998
		BG 99710 A	31-01-1996
		CA 2110670 A	12-06-1994
		CN 1092071 A,B	14-09-1994
		CZ 9501514 A	13-12-1995
		FI 952863 A	09-06-1995
		HU 9500324 A	28-09-1995
		HU 72076 A	28-03-1996
		JP 2509530 B	19-06-1996
		JP 6263737 A	20-09-1994
		KR 203962 B	15-06-1999
		MX 9307850 A	30-06-1994
		NO 952295 A	10-08-1995
		NZ 258412 A	29-01-1997
		PL 309331 A	02-10-1995
		SI 9300646 A	30-09-1994
		SK 75995 A	08-11-1995
		WO 9413696 A	23-06-1994
		US 5652235 A	29-07-1997
		AT 178070 T	15-04-1999
		AU 673017 B	24-10-1996
		AU 5232193 A	23-06-1994
		BR 1100850 A	07-12-1999
		CA 2110672 A	12-06-1994
		CN 1092767 A,B	28-09-1994
		CZ 9501515 A	13-12-1995
		DE 69324148 D	29-04-1999
		DE 69324148 T	28-10-1999
		EP 0662481 A	12-07-1995
		ES 2129072 T	01-06-1999
		FI 952862 A	09-06-1995
		HR 931484 A	30-04-1996
		HU 73228 A	29-07-1996
		IL 107836 A	04-01-1998
		JP 2509147 B	19-06-1996
		JP 7097367 A	11-04-1995
		MX 9307851 A	30-06-1994
		NO 952294 A	10-08-1995
		NZ 258429 A	26-05-1997
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		SI 9300647 A	30-09-1994
		WO 9419367 A	01-09-1994
		US 5578593 A	26-11-1996
		ZA 9309272 A	08-08-1994
		ZA 9309274 A	08-08-1994
WO 9816527 A	23-04-1998	AU 6708298 A	11-05-1998
		WO 9851687 A	19-11-1998
US 5721250 A	24-02-1998	US 5492916 A	20-02-1996
		AU 1172995 A	29-05-1995
		BG 100555 A	31-10-1996
		BR 9408019 A	26-08-1997
		CA 2175218 A	18-05-1995
		CN 1174504 A	25-02-1998
		CZ 9601342 A	11-12-1996

INTERNATIONAL SEARCH REPORT

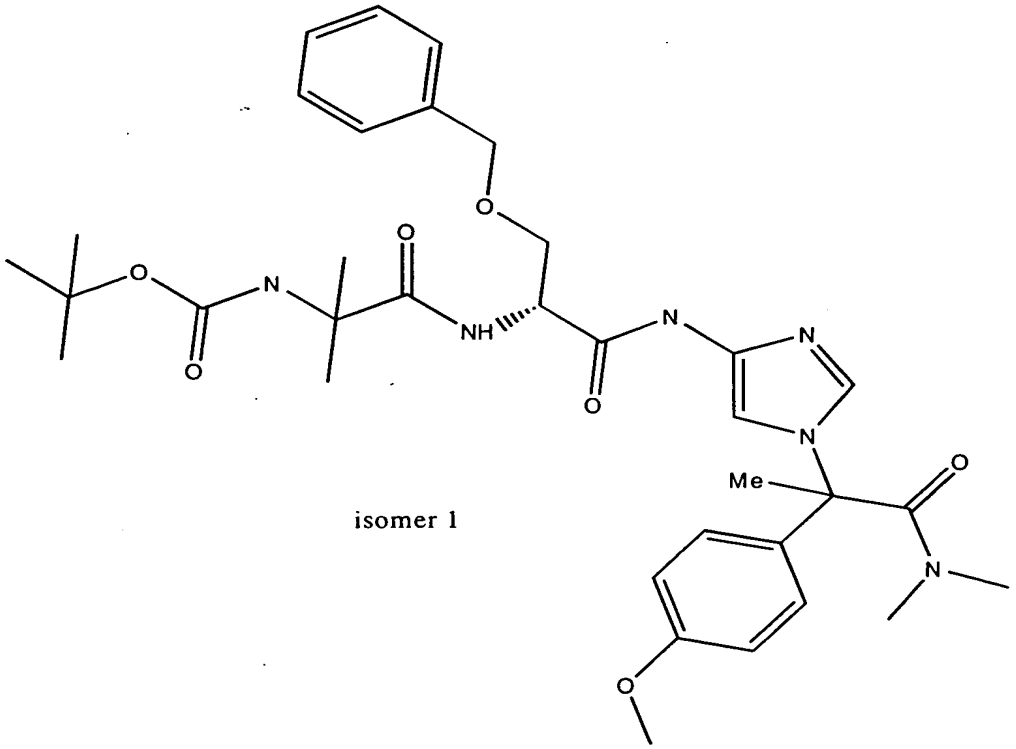
Information on patent family members

International Application No
PCT/US 00/04274

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5721250 A		EP 0739204 A	30-10-1996
		FI 961951 A	08-05-1996
		HU 74733 A	28-02-1997
		JP 10506091 T	16-06-1998
		LV 11525 A	20-10-1996
		LV 11525 B	20-02-1997
		NO 961865 A	08-07-1996
		PL 322706 A	16-02-1998
		SK 56296 A	05-02-1997
		WO 9513069 A	18-05-1995
		US 5622973 A	22-04-1997

Prepared as in Preparation 17 using the product of Preparation EX9A, diastereomer 1 (2.31 g, 5.15 mmol) in THF (50 mL) and lithium hydroxide (0.26 g, 6.18 mmol) in water (25 mL) to give the crude acid. The resulting crude solid was dissolved in anhydrous dichloromethane (50 mL) and reacted with catalytic DMF (0.1 mL) and excess oxalyl chloride (5 g) to give the crude acid chloride. The resulting crude foam was dissolved in anhydrous dichloromethane (50 mL) and reacted with 4-Dimethylaminopyridine (catalytic, 10 mg) and dimethylamine (2.0 M in THF, 7.7 mL, 15.46 mmol) to yield the desired product (1.57 g, 96% yield) as a colorless foam: ^{1}H NMR (300 MHz, $CDCl_3$) - consistent with structure; Anal. calc'd. for $C_{15}H_{18}N_4O_4$; 56.60 C, 5.70 H, 17.60 N; found 57.04 C, 6.09 H, 16.82 N; ISMS (M+) - 319.

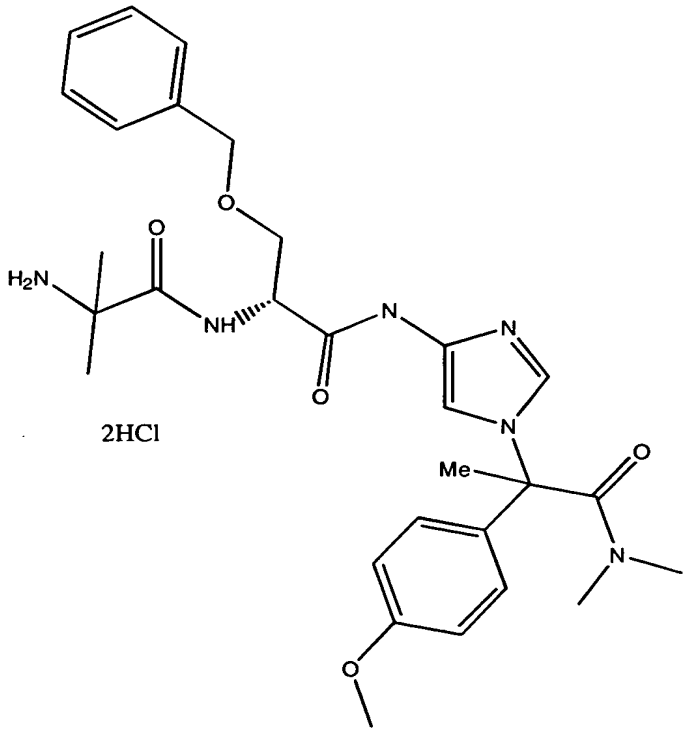
Preparation 45



isomer 1

Prepared as in Preparation EX2B using the product of Preparation 21 (0.75 g, 2.36 mmol) and 5% palladium on carbon (0.80 g, catalytic, 25 mL THF) to give the crude amine. The resulting filtrate was reacted with HOBT (0.32 g, 2.36 mmol), the product of Preparation 1 (0.90 g, 2.36 mmol), and DCC (0.54 g, 2.60 mmol) to yield the desired product (0.86 g, 56% yield) as a light yellow foam: ^{1}H NMR (300 MHz, $CDCl_3$) - consistent with structure; Anal. calc'd. for $C_{37}H_{50}N_6O_6$; 62.75 C, 7.12 H, 12.91 N; found 62.65 C, 6.95 H, 12.76 N; ISMS (M+) - 651.

Compound 54

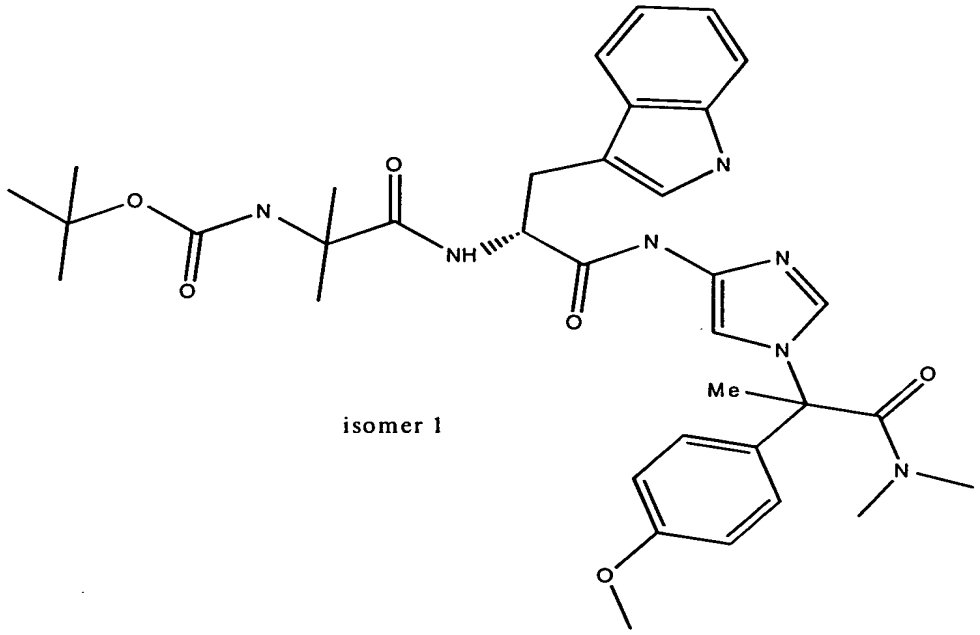


Prepared as in Example 2-7 using the product of Preparation 45 (0.84 g, 1.29 mmol), trifluoroacetic acid (4.0 mL), anisole (0.4 mL), and dichloromethane (20 mL) to yield the desired product (0.69 g, 86%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) - consistent with structure;

Anal. calc'd. for $C_{29}H_{38}N_6O_5Cl_2$; 55.86 C, 6.47 H, 13.48 N; found 55.31 C, 6.52 H, 13.01 N; ISMS (M+) - 551.

Example 2-40

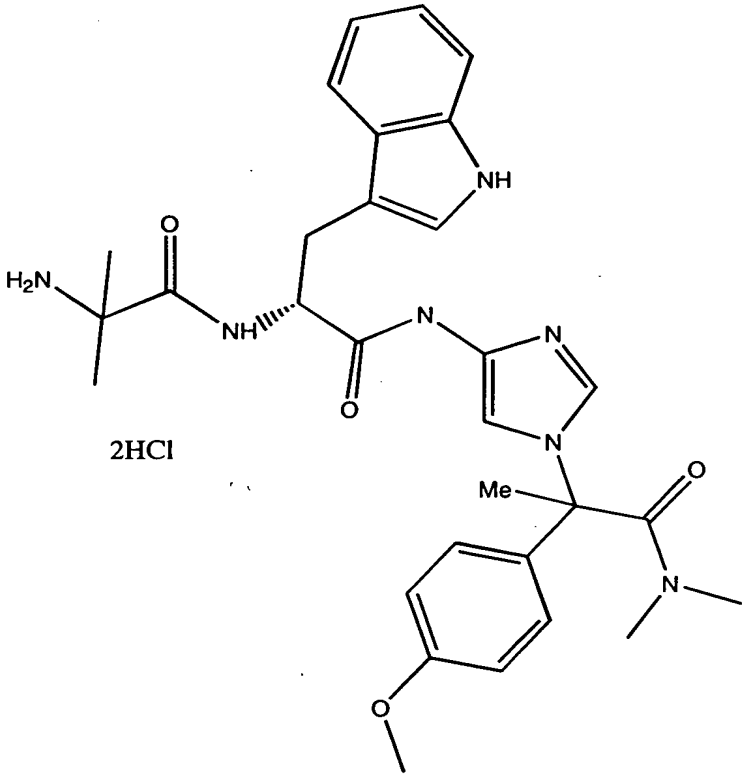
Preparation 46



isomer 1

Prepared as in Preparation EX2B using the product of Preparation 21 (0.80 g, 2.52 mmol) and 5% palladium on carbon (0.80 g, catalytic, 25 mL THF) to give the crude amine. The resulting filtrate was reacted with HOBT (0.34 g, 2.52 mmol), the product of Preparation 37 (0.99 g, 2.52 mmol), and DCC (0.57 g, 2.77 mmol) to yield the desired product (0.77 g, 46% yield) as a light yellow foam: ^{1}H NMR (300 MHz, $CDCl_3$) - consistent with structure; Anal. calc'd. for $C_{37}H_{50}N_6O_6$; 63.72 C, 6.87 H, 14.86 N; found 63.45 C, 6.86 H, 14.76 N; ISMS (M+) - 660.

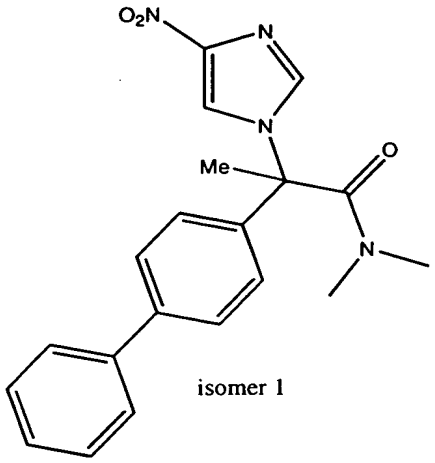
Compound 55



Prepared as in Example 2-7 using the product of Preparation 46 (0.75 g, 1.13 mmol), trifluoroacetic acid (4.0 mL), anisole (0.4 mL), and dichloromethane (20 mL) to yield the desired product (0.62 g, 87%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) - consistent with structure; Anal. calc'd. for $C_{30}H_{37}N_7O_4Cl_2$; 56.96 C, 6.21 H, 15.50 N; found 55.48 C, 6.03 H, 14.63 N; ISMS (M+) - 560.

Example 2-41

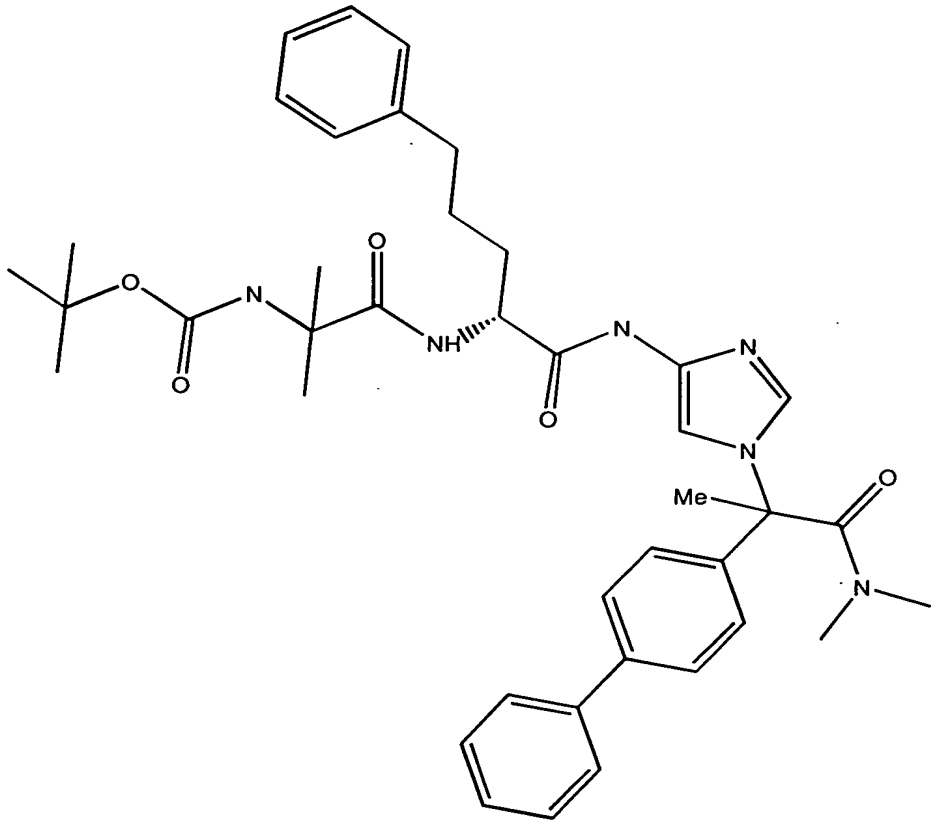
Preparation 24



isomer 1

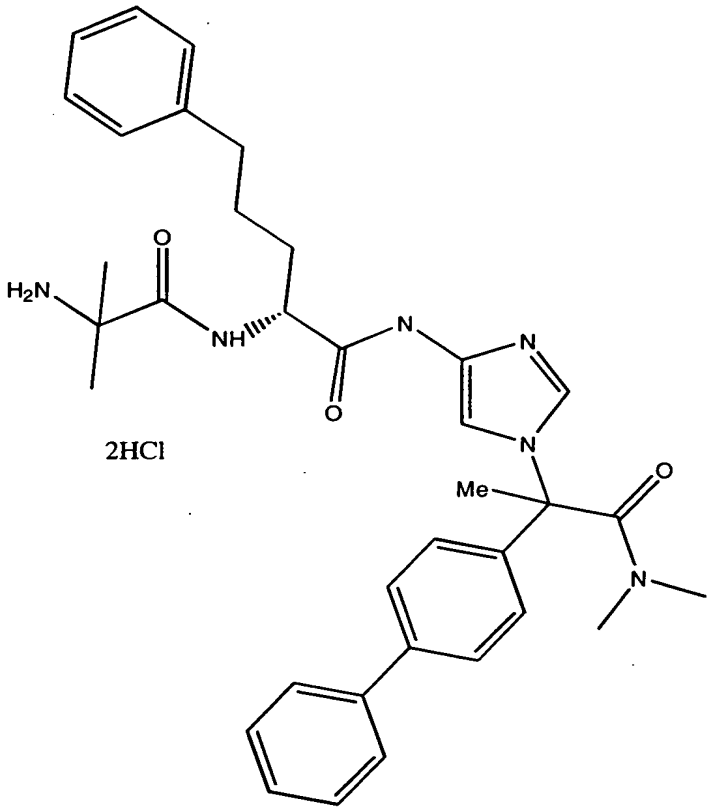
Prepared as in Preparation EX2A using the product of Preparation 12B, diastereomer 1 (0.50 g, 1.00 mmol) in THF (20 mL) and lithium hydroxide (0.05 g, 1.10 mmol) in water (10 mL) to give the crude acid. The resulting crude solid was dissolved in anhydrous dichloromethane (50 mL) and reacted with catalytic DMF (0.1 mL) and excess oxalyl chloride (5 g) to give the crude acid chloride. The resulting crude foam was dissolved in anhydrous dichloromethane (50 mL) and reacted with 4-Dimethylaminopyridine (catalytic, 10 mg), N-methylmorpholine (0.33 mL, 3.00 mmol), and dimethylamine hydrochloride (0.13 g, 1.50 mmol) to yield the desired product (0.30 g, 82% yield) as a colorless foam: ^{1}H NMR (300 MHz, $CDCl_3$) - consistent with structure; Anal. calc'd. for $C_{20}H_{20}N_4O_3$; 65.92 C, 5.53 H, 15.37 N; found 64.17 C, 5.41 H, 14.15 N; ISMS (M+) - 365.

Preparation 50



Prepared as in Preparation EX2B using the product of Preparation 24 (0.30 g, 0.82 mmol) and 5% palladium on carbon (0.30 g, catalytic, 25 mL THF) to give the crude amine. The resulting filtrate was reacted with HOBT (0.11 g, 0.82 mmol), the product of Preparation 2 (0.31 g, 0.82 mmol), and DCC (0.19 g, 0.90 mmol) to yield the desired product (0.32 g, 56% yield) as a light yellow foam: ^{1}H NMR (300 MHz, $CDCl_3$) - consistent with structure; Anal. calc'd. for $C_{40}H_{50}N_6O_5$; 69.14 C, 7.25 H, 12.09 N; found 67.82 C, 7.07 H, 11.62 N; ISMS (M+) - 695.

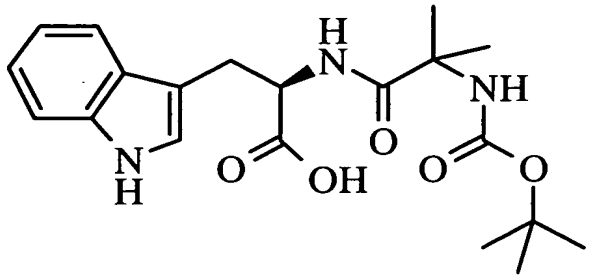
Compound 56



Prepared as in Example 2-7 using the product of Preparation 50 (0.32 g, mmol), trifluoroacetic acid (4.0 mL), anisole (0.4 mL), and dichloromethane (20 mL) to yield the desired product (0.26 g, %) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) - consistent with structure; Anal. calc'd. for $C_{35}H_{44}N_6O_3Cl_2$; 62.96 C, 6.64 H, 12.59 N; found 60.05 C, 6.31 H, 11.98 N; FDMS (M+) - 595.

Example 2-42

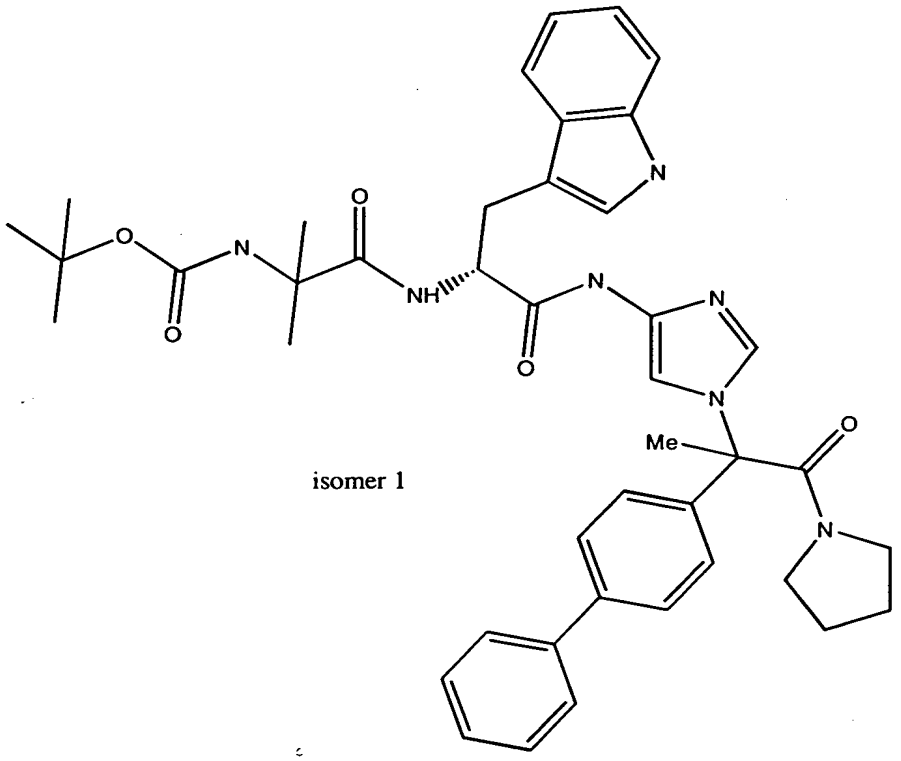
Preparation 37



N-Methyl morpholine (4.79 mL, 2 eq, 47.3 mm) was added to a stirred slurry of *N*-Boc-a-aminoisobutyric acid (4.43 g, 21.7 mm, 1 eq) and 3.89 g (21.7 mm, 1.0 eq) of 2-chloro-(4,6)-dimethoxy-1,3,5-triazine (CDMT) in 100 mL of diethyl ether. After stirring the reaction mixture at ambient temperature for 1.5 hours, D-tryptophan ester hydrochloride was added. After stirring overnight, the reaction mixture was quenched by the addition of 150 mL of 10% aqueous citric acid solution. The layers were separated and the ether layer was washed with 50 mL of saturated sodium bicarbonate solution and 50 mL of water. Lithium hydroxide (2.43 g, 5 eq) was dissolved in 100 ml of water and the solution was added to the diethyl ether solution and stirred vigorously for 4 hours at room temperature. The layers were separated and the pH of the aqueous layers was adjusted to 5.6 with 1M HCl. The pH was then adjusted to 3.95 with 10% citric acid solution and the aqueous layer was extracted with 100 mL of ethyl acetate. The ethyl acetate layers were washed with brine, dried over magnesium sulfate and filtered. The volatiles were removed under vacuum to give 82 % yield of

the desired product as a white foam. 1H-NMR consistent with structure.

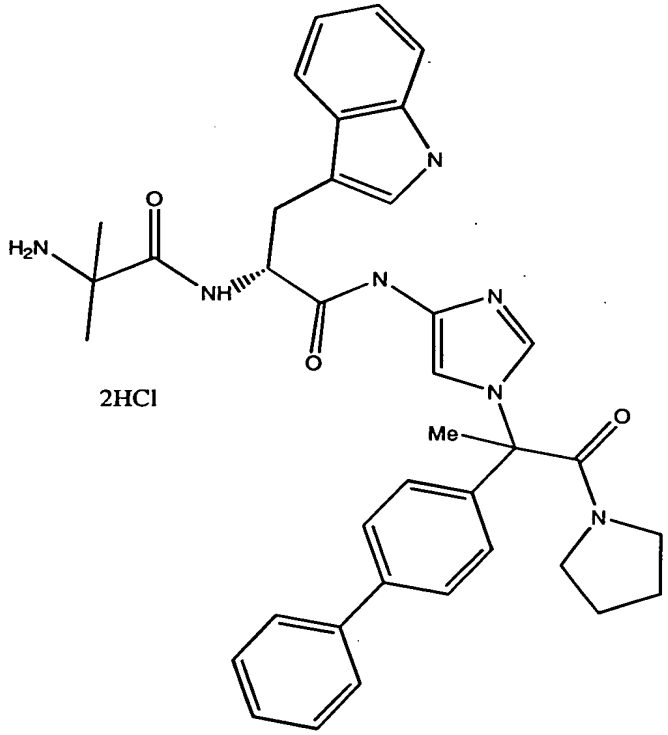
Preparation 49



isomer 1

Prepared as in Preparation EX2B using the product of Preparation EX17A (0.20 g, 0.51 mmol) and 5% palladium on carbon (0.20 g, catalytic, 25 mL THF) to give the crude amine. The resulting filtrate was reacted with HOBT (0.07 g, 0.51 mmol), the product of Preparation 37 (0.20 g, 0.51 mmol), and DCC (0.12 g, 0.51 mmol) to yield the desired product (0.17 g, 45% yield) as a light yellow foam: ^{1}H NMR (300 MHz, $CDCl_3$) - consistent with structure; Anal. calc'd. for $C_{42}H_{49}N_7O_6$; 68.93 C, 6.75 H, 13.40 N; found 67.02 C, 6.54 H, 12.71 N; ISMS (M+) - 732.

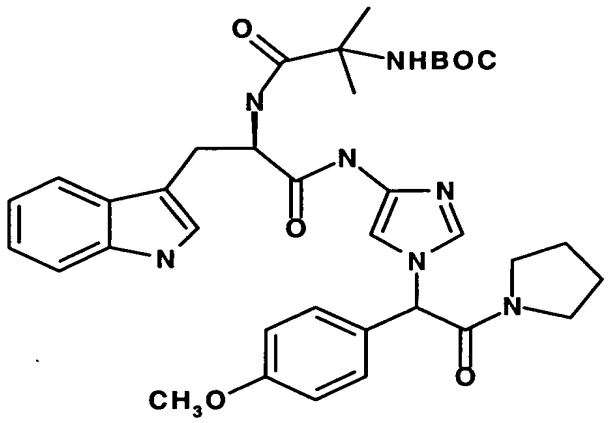
Compound 57



Prepared as in Example 2-7 using the product of Preparation 49 (0.96 g, 1.31 mmol), trifluoroacetic acid (4.0 mL), anisole (0.4 mL), and dichloromethane (20 mL) to yield the desired product (0.54 g, 59%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) - consistent with structure; Anal. calc'd. for $C_{37}H_{43}N_7O_3Cl_2$; 63.06 C, 6.15 H, 13.91 N; found 58.22 C, 5.48 H, 12.32 N; ISMS (M+) - 632.

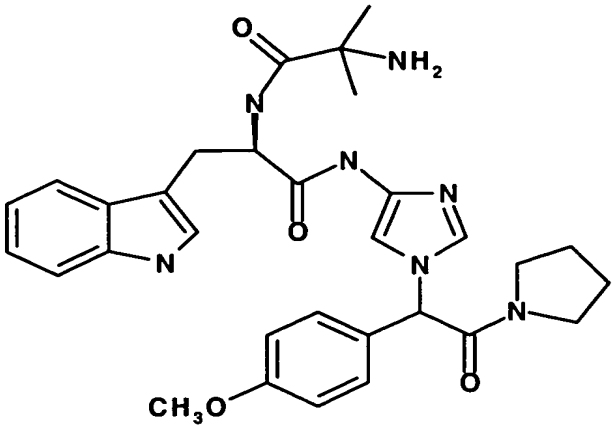
Example 2-43

Preparation 15



The product of Preparation EX9A (0.85 g, 2.57 mmol) was combined with 10% palladium/carbon (0.50 g) and palladium/black (0.15 g) in tetrahydrofuran (40 mL)and the mixture shaken under a hydrogen atmosphere (38 psi) in a Parr apparatus. After reduction was complete, the catalyst was removed by filtration through celite and the amine/tetrahydrofuran solution was immediately combined with 1,3-dicyclohexylcarbodiimide (0.53 g, 2.57mmol), 1-hydroxybenzotriazole (0.35 g, 2.57 mmol), the product of Preparation 1L (1.00 g, 2.57 mmol) and additional tetrahydrofuran (60 mL). After stirring overnight at ambient temperature, the mixture was concentrated and the residue slurried in ethyl acetate and filtered. The filtrate was concentrated and the residue purified by flash chromatography(silica gel, chloroform/methanol) which gave 1.62 g of the desired product which was used without further purification.

Compound 58

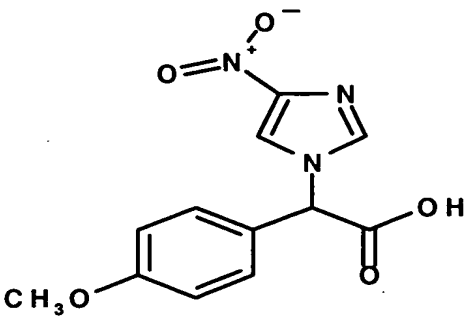


The compound of Preparation 15 (1.57 g, 2.34 mmol) was dissolved in dichloromethane (25 mL) and triflouroacetic acid (10 mL) added. The resulting mixture was stirred at ambient temperature for 2.5 h, concentrated, and the residue treated with excess aqueous sodium bicarbonate. The aqueous mixture was extracted with ethyl acetate and the combined organic extracts concentrated and dried. The residue was chromatographed over silica gel (chloroform/methanol) to provide 0.71 g (53 %) of the desired product: MS: $(M+H)^+$ 572.5. ^1H NMR was consistent with product. *Anal.* Calcd. for $C_{31}H_{37}N_7O_4 \cdot 0.35\ CHCl_3$: C, 61.38; H, 6.14; N, 15.98. Found: C, 61.36; H, 6.11; N, 16.08. The isomeric mixture (2.16 g) was separated as previously described in Example 6 to provide 1.10 g of isomer 1 (t_R = 10.34 min) and 0.80 g of isomer 2 (t_R = 13.70 min). The product derived from isomer 2 (0.80 g, 1.40 mmol) was dissolved in a minimal amount of ethyl acetate and the resulting solution treated with an excess of hydrochloric acid in ethyl acetate. The solution was then concentrated to provide 0.88 g (82 %) of the desired product as an off white solid: MS: $(M+H)^+$ 572.3, 573.4. ^1H NMR was consistent with product. *Anal.*

Calcd. For$C_{31}H_{37}N_7O_4 \cdot 3.0$ HCl: C, 54.67; H, 5.92; N, 14.40. Found: C, 54.25; H, 5.89; N, 13.35.

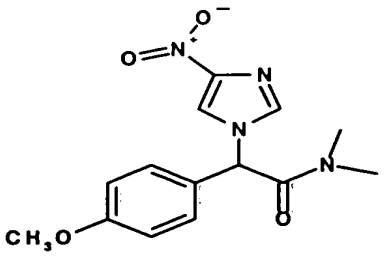
Example 2-44

Preparation 16



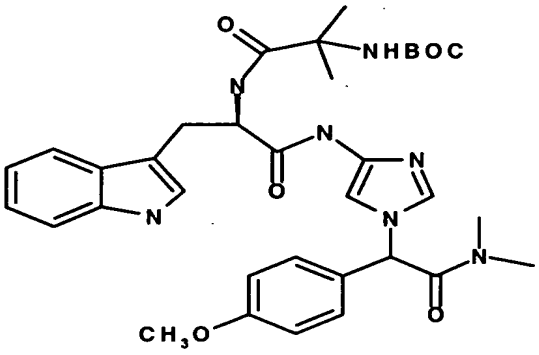
To a solution of the product of Preparation 4 (5.75 g,18.9 mmol) stirring at room temperature in tetrahydrofuran (10 mL) was added sodium hydroxide (25 mL of a 5 N aqueous solution) along with water (15 mL) and ethanol (10 mL). After hydrolysis was complete, the mixture was acidified to pH 2.0 with aqueous hydrochloric acid and extracted. The combined organic extracts were dried, filtered, and concentrated to give the desired product in quantitative yield as a tan solid: ^{1}H NMR (300 MHz,DMSO-d_6) δ 14.05-13.60 (bs, 1H), 8.34 (s, 1H) 7.90 (s, 1H), 7.45 (d, 2H, J = 8.67 Hz), 7.00 (d, 2H, J = 8.67 Hz), 6.42 (s, 1H), 3.77 (s, 3H). FDMS: 277 $(M)^+$ *Anal.* Calcd. for $C_{12}H_{11}N_3O_5 \cdot 0.67\ H_2O$: C, 49.82; H, 4.30;N, 14.52. Found: C, 50.05; H, 4.01; N, 14.12.

Preparation 17



The compound of Preparation 16 (2.50 g,9.0 mmol) was combined with aqueous dimethylamine(40%,1.15 mL,9.0 mmol), 1-hydroxy-benzotriazole hydrate(1.22 g, 9.0 mmol)and 1,3-dicyclohexylcarbodiimide (1.86 g, 9.0 mmol) in tetrahydrofuran (60 mL) and the mixture stirred at ambient temperature. After 18 h, the mixture was concentrated and the residue slurried in ethyl acetate and filtered. The filtrate was concentrated and the resulting residue purified by flash chromatography (silica gel, chloroform/methanol) to afford 1.83 g (67%) of the desired product: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (s, 1H) 7.76 (s, 1H), 7.42 (d, 2H, J = 8.67 Hz), 7.00 (d, 2H, J = 8.67 Hz), 6.78 (s, 1H), 3.77 (s, 3H), 2.91 (2, 3H), 2.85 (s, 3H). ESMS: $(M+H)^+$ 305.2.

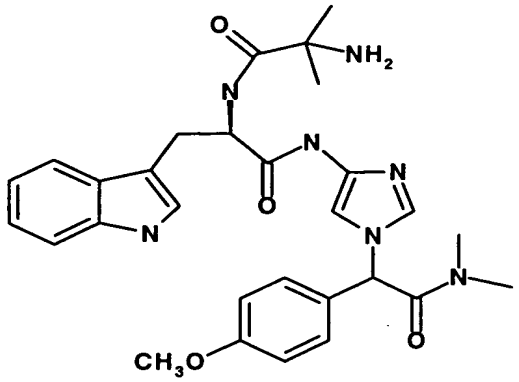
Preparation 19



The compound of preparation 17 (0.73 g, 2.38 mmol) was combined with 10% palladium/carbon (0.50 g) and palladium/black (0.10 g) in tetradyrofuran(40 mL)and the mixture shaken under hydrogen (38 psi) in a Parr apparatus. After reduction was complete, the catalyst was removed by filtration through celite and the resulting solution was immediately combined with dicyclohexylcarbodiimide (0.49 g, 2.38 mmol), 1-hydroxybenzotriazole mono-hydrate (0.32 g, 2.37 mmol), the product of Preparation 1L (0.93 g, 2.39 mmol) and

additional tetrahydrofuran (60 mL). After stirring overnight at ambient temperature, the mixture was concentrated and the residue slurried in ethyl acetate and filtered. The filtrate was concentrated and the residue purified by silica gel chromatography (chloroform/methanol) to provide 0.76 g (50%) of the desired product as an off white solid which was used without further purification.

Compound 59

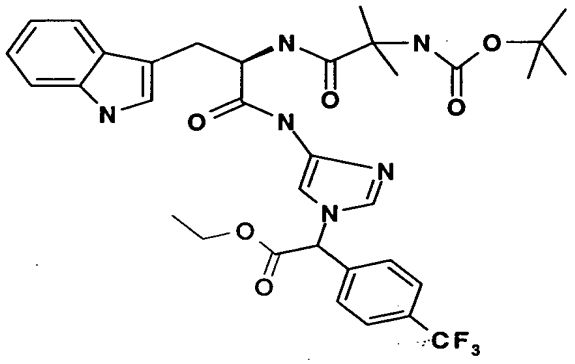


To a solution of the compound of preparation 19 (0.74 g, 1.15 mmol) stirring at room temperature in dichloromethane (30 mL) was added triflouroacetic acid (10 mL). After 2 h, the mixture was concentrated and the residue treated with excess aqueous sodium bicarbonate. The resulting mixture was extracted with ethyl acetate and the combined organic extracts were concentrated. The residue was purified by flash chromatography (silica gel, chloroform/methanol) to provide 0.23 g (37%) of the desired product: ESMS: $(M+H)^+$ 546.6. ^1H NMR was consistent with product. *Anal.* Calcd. for $C_{29}H_{35}N_7O_4 \cdot 0.25$ CHCl3: C, 61.05; H, 6.17; N, 17.04. Found: C, 61.41; H, 6.32; N, 16.52. The isomeric mixture (2.00 g) was separated as described in Example 10 to provide 0.73 g of

isomer 1 (t_R = 9.85 min) and 0.82 g of isomer 2 (t_R = 12.87 min). To a solution of isomer 2 (0.82 g, 1.50 mmol) stirring in ethyl acetate and methanol was added a saturated solution of hydrochloric acid in ethyl acetate. The resulting mixture was concentrated to provide 0.84 g of the desired product: ESMS: $(M+H)^+$ 546.2, 547.3. ^1H NMR was consistent with product. *Anal*. Calcd. for $C_{29}H_{35}N_7O_4 \cdot 3.0$ HCl: C, 53.18; H, 5.85; N, 14.97. Found: C, 53.73; H, 6.03; N, 14.04.

Example 2-45

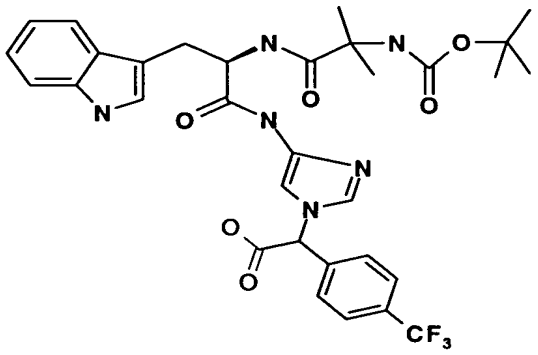
Preparation 34



Hydrogenation of the product of Preparation 8 (1.75 g, 5.1 mmol) with 10% palladium on carbon (1.4 g) in tetrahydrofuran (60 mL) followed by reaction with the product of Preparation 1L (2.0 g, 5.1 mmol), 1-hydroxybenzotriazole (0.76 g, 5.6 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.16 g, 5.6 mmol) as described in Preparation 5A gave 2.51 g (72%) of the desired product as a tan foam: ^1H-NMR (d, DMSO) 1.15-1.35 (m, 18H), 3.05-3.15 (m, 2H), 4.25 (m, 2H), 4.65 (br s, 1H), 6.62 (s, 1H), 6.85 (m, 1H), 6.95-7.08 (m, 2H), 7.20-7.30 (m, 2H), 7.40-7.55 (m, 2H), 7.55-7.65 (m, 3H), 7.82 (d, J = 8.3 Hz, 2H), 10.20 (br s, 1H), 10.75 (br s, 1H); MS (ion spray) 685 (M+1); Anal. Calc'd for

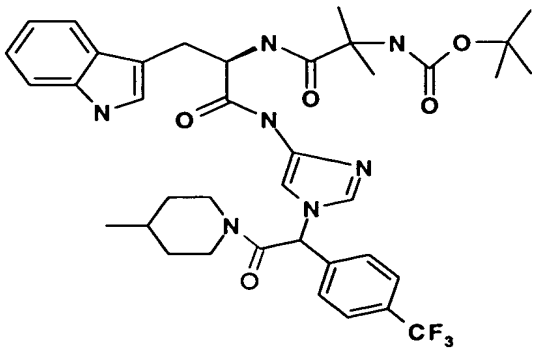
$C_{34}H_{39}F_3N_6O_6 \cdot 1H_2O$: C, 58.11; H, 5.88; N, 11.96. Found: C, 58.15; H, 5.59; N, 11.92.

Preparation 35



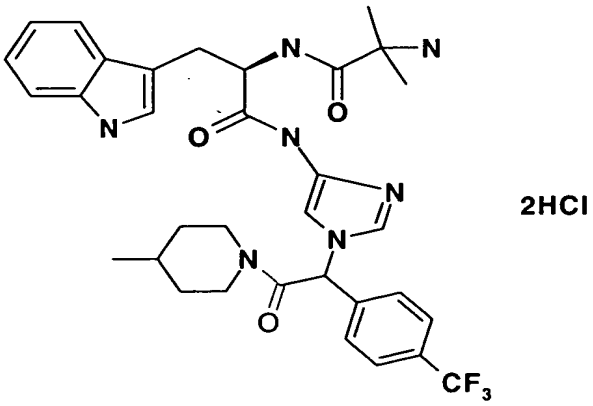
Reaction of the product of Preparation 34 (2.2 g, 3.2 mmol) and lithium hydroxide (0.1 g, 3.9 mmol) in dioxane (50 mL) and water (25 mL) as described in Preparation 5 gave 2.1 g (100%) of the desired product as a tan foam: ^{1}H-NMR (d, DMSO), 1.15-1.35 (m, 15H), 3.05-3.15 (m, 2H), 4.65 (br s, 1H), 6.97 (s, 1H), 6.90 (m, 1H), 6.98-7.10 (m, 2H), 7.20-7.30 (m, 2H), 7.40-7.55 (m, 2H), 7.57-7.64 (m, 3H), 7.80 (d, J = 8.3 Hz, 2H), 10.20 (br s, 1H), 10.75 (br s, 1H), 13.80 (br s, 1H); MS (ion spray) 657.4 (M+1); Anal. Calc'd for $C_{32}H_{35}F_3N_6O_6$: C, 58.53; H, 5.37; N, 12.80. Found: C, 59.28; H, 5.17; N, 12.65.

Preparation 36



Reaction of the product of Preparation 35 (0.7 g, 1.1 mmol), 4-methylpiperidine (0.13 mL, 1.1 mmol), 1-hydroxybenzotriazole (0.17 g, 1.2 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.26 g, 1.2 mmol) in N,N-dimethylformamide (30 mL) as described in Preparation EX4A provided 0.47 g (58%) of the desired product as a tan foam: ^{1}H-NMR (d, DMSO) 0.78 (d, J = 6.4 Hz, 1.5H), 0.86 (d, J = 6.3 Hz, 1.5H), 1.15-1.35 (m, 18H), 1.50-1.70 (m, 3H), 2.60-2.70 (m, 2H), 3.00-3.15 (m, 2H), 3.30 (m, 1H), 4.40 (m, 1H), 4.65 (m, 1H), 6.85-6.95(m, 2H), 7.00-7.10 (m, 2H), 7.17-7.30 (m, 2H), 7.40-7.60 (m, 4H), 7.75-7.85 (m, 2H), 10.20 (br s, 1H), 10.75 (br s, 1H); MS (ion spray) 738.5 (M+1); Anal. Calc'd for $C_{38}H_{46}F_3N_7O_5 \cdot 1H_2O$: C, 60.39; H, 6.40; N, 12.97. Found: C, 60.18; H, 6.21; N, 12.99.

Compounds 60 and 61



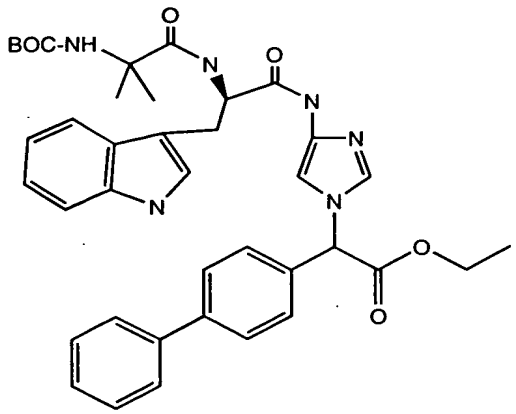
2HCl

Reaction of the product of Preparation 36 (4.8 g, 6.5 mmol) and trifluoroacetic acid (16 mL) in dichloromethane (40 mL) as described in Example 4 gave 2.0 g (44%) of the desired mixture as a tan foam. Purification by HPLC (8 x 15 cm Prochrom column packed with Kromasil CHI-DMP chiral phase with an eluent mixture of 3A alcohol (13% by v), dimethylethylamine (0.2% by v) in heptane at a flow rate of 250 mL/min) gave 0.5 g (12

%) of isomer 1 and 0.4 g (9 %) of isomer 2. **Compound 60 (isom r 1)** ^{1}H-NMR (d, DMSO) 0.77 (d, J = 6.5 Hz, 1.5H), 0.87 (d, J = 6.0 Hz, 1.5H), 1.00 (m, 1H), 1.32 (s, 3H), 1.50 (s, 3H), 1.50-1.70 (m, 2H), 2.72 (m, 1H), 3.00-3.30 (m, 4H), 3.75 (m, 1H), 4.05-4.33 (m, 3H), 4.20 (m, 1H), 4.78 (m, 1H), 6.94 (m, 3H), 7.20 (s, 1H), 7.30-7.40 (m, 2H), 7.55-7.70 (m, 2H), 7.75-8.00 (m, 4H), 8.05-8.15 (m, 2H), 8.50 (m, 1H), 10.86 (s, 1H), 11.05 (s, 1H); t_R = 6.01 min; MS (ion spray) 638.2 (M+1). **Compound 61 (isomer 2)** ^{1}H-NMR (d, DMSO) 0.77 (d, J = 6.5 Hz, 1.5H), 0.87 (d, J = 6.0 Hz, 1.5H), 1.00 (m, 1H), 1.32 (s, 3H), 1.50 (s, 3H), 1.50-1.70 (m, 2H), 2.72 (m, 1H), 3.00-3.30 (m, 4H), 3.75 (m, 1H), 4.05-4.33 (m, 3H), 4.20 (m, 1H), 4.78 (m, 1H), 6.94 (m, 3H), 7.20 (s, 1H), 7.30-7.40 (m, 2H), 7.55-7.70 (m, 2H), 7.75-8.00 (m, 4H), 8.05-8.15 (m, 2H), 8.50 (m, 1H), 10.86 (s, 1H), 11.05 (s, 1H); t_R = 7.5 min; MS (ion spray) 638.2 (M+1).

Example 2-46

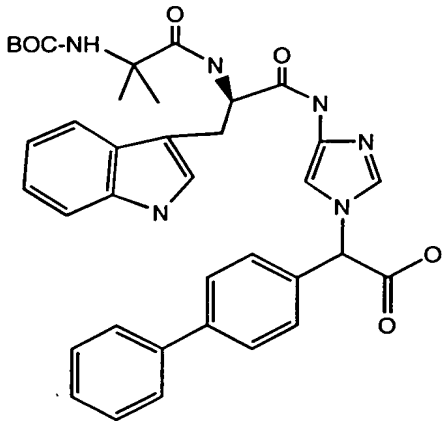
Preparation 345



To a mixture of the product of Preparation 11 (6.0 g, 17.1 mmol) and 10% palladium on carbon (6.0 g) in tetrahydrofuran (100 mL). The reaction mixture was placed under a hydrogen atmosphere (40 psi) using a Parr

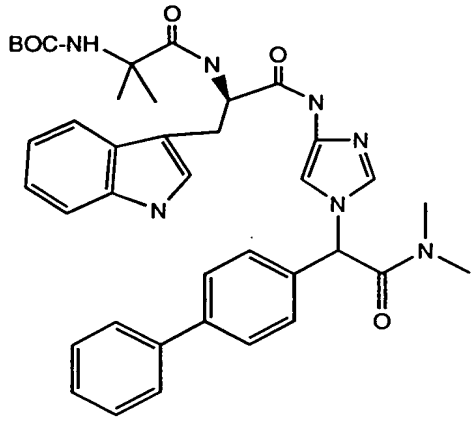
apparatus for 30 min then filtered through Celite. The resulting solution was then added to a previously prepared mixture of the product of Preparation 1L (6.66 g, 17.1 mmol), 1-hydroxybenzotriazole (2.31 g, 17.1 mmol), and 1,3 dicyclohexylcarbodiimide (3.53 g, 17.1 mmol) in tetrahydrofuran (75 mL). After 16 h at room temperature, the reaction mixture was concentrated and the crude material purified by flash chromatography (silica gel, 4% methanol/dichloromethane) to yield 6.17 g (52%) of the desired product as a brown foam: ^{1}H NMR consistent with structure; MS (ion spray) 693 (M+1).

Preparation 346



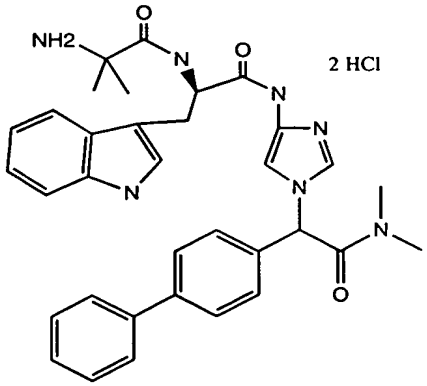
To a solution of the product Preparation 345 (4.6 g, 6.64 mmol) stirring in tetrahydrofuran (100 mL) at room temperature was added a solution of lithium hydroxide in water (40 mL of 1M). After 30 min, the reaction mixture was acidified with 5N HCl (8.5 mL). The resulting mixture diluted with water and exttraced with ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated to yield 4.4 g (99%) of the desired product as a yellow foam.

Preparation 347



To a solution of the product Preparation 346 (4.0 g, 6.02 mmol) stirring in tetrahydrofuran (50 mL) at room temperature was added 1-hydroxybenzotriazole (813 mg, 6.02 mmol) and 1,3 dicyclohexylcarbodiimide (1.24 g, 6.02 mmol). After 15 min, dimethylamine (3.0 mL of a 2M soln in tetrahydrofuran, 6.02 mmol) was added. After stirring for 16 h in a sealed flask, the reaction mixture was filtered and concentrated. The resulting crude material was purified by flash chromatography (silica gel, 5% methanol/dichloromethane) to yield 2.79 g (68%) of the desired product as a yellow foam..

Compounds 62 and 63



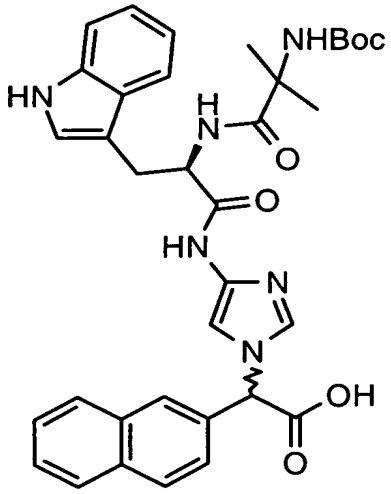
To the product of Preparation 347 (3.4 g, 5.0 mmol) was added a saturated solution of HCl(g)/acetic acid (50 mL). After 1.5 h, the reaction mixture was concentrated then partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was removed, dried over sodium sulfate and concentrated to yield 2.45 g (84%) of the free base as a light yellow foam. The diastereomeric material (2.45 g) was chromatographed on an 8 x 15 cm Prochrom column packed with Kromsil CHI chiral phase using an eluent mixture of 3A alcohol and dimethylethylamine in heptane to provide the individual diastereomers in pure form: ^{1}H NMR consistent with product; MS (ion spray) 592 (M+1); Anal. Calcd. for $C_{34}H_{37}N_7O_3$: C, 69.02; H, 6.30; N, 16.57. (Found) C, 67.93; H, 6.29; N, 15.80.

Compound 62 (Isomer 1) To a solution of the purified isomer in ethyl acetate was added a saturated solution of hydrochloric acid in ethyl acetate. The resulting slurry was concentrated to dryness to yield 992 mg (37%) of the desired product as an off-white solid: ^{1}H NMR consistent with product; MS (ion spray) 592 (M+1); Anal. Calcd. for $C_{34}H_{37}N_7O_3$ x 2 HCl: C, 61.44; H, 5.91; N, 14.75. (Found) C, 59.54; H, 5.92; N, 13.76.

Compound 63 (Isomer 2) To a solution of the purified isomer in ethyl acetate was added a saturated solution of hydrochloric acid in ethyl acetate. The resulting slurry was concentrated to dryness to yield 1.17 g (40%) of the desired product as an off-white solid: ^{1}H NMR consistent with structure; MS (ion spray) 592 (M+1); Anal. Calcd. for $C_{34}H_{37}N_7O_3$ x 2 HCl: C, 61.44; H, 5.91; N, 14.75. (Found) C, 59.03; H, 6.04; N, 13.84.

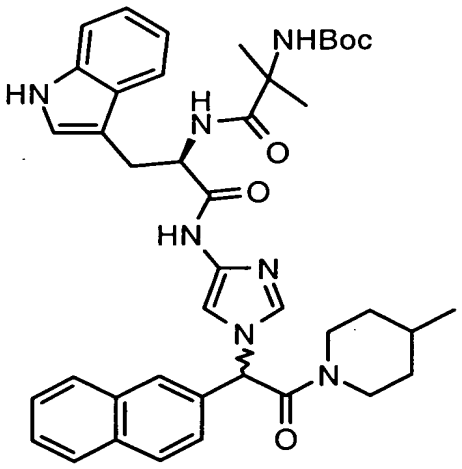
Example 2-47

2-[4-((2R)-2-{2-[(Tert-butoxy)carbonylamino]-2-methylpropanoylamino}-3-indol-3-ylpropanoylamino)imidazolyl]-2-(2-naphthyl)acetic Acid



A solution consisting of ethyl 2-[4-((2R)-2-{2-[(tert-butoxy)carbonylamino]-2-methylpropanoylamino}-3-indol-3-ylpropanoylamino)imidazolyl]-2-(2-naphthyl)acetate (1.52 grams, 2.28 mmol), lithium hydroxide (0.11 grams, 4.56 mmol), dioxane (10 mL), and water (10 mL) was stirred at ambient temperature until complete as determined by hplc (30 minutes). The reaction mixture was concentrated to dryness and the residue was dissolved in water (20 mL). The aqueous solution was adjusted to a pH of 3 using a 10% sodium bisulfate solution and extracted with ethyl acetate (3 x 25 mL). The organic layers were combined, dried using sodium sulfate, filtered, and concentrated to give 1.34 grams (92%) of 2-[4-((2R)-2-{2-[(tert-butoxy)carbonylamino]-2-methyl propanoylamino}-3-indol-3-ylpropanoylamino)imidazolyl]-2-(2-naphthyl)acetic acid.

N-[(1R)-2-Indol-3-yl-1-(N-{1-[2-(4-methylpiperidinyl)-1-(2-naphthyl)-2-oxoethyl]imidazol-4-yl}carbamoyl)ethyl]-2-[(tert-butoxy)carbonylamino]-2-methylpropanamide

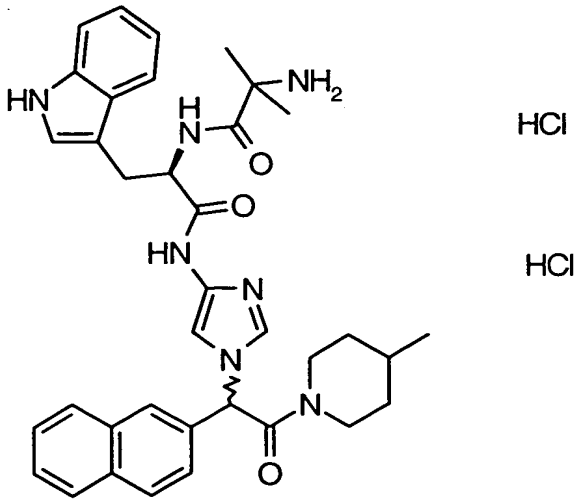


A solution consisting of 2-[4-((2R)-2-{2-[(tert-butoxy)carbonylamino]-2-methylpropanoylamino}-3-indol-3-yl propanoylamino)imidazolyl]-2-(2-naphthyl)acetic acid (0.55 grams, 0.861 mmol), 4-methylpiperidine (0.085 grams, 0.861 mmol), 1,3-dicyclohexylcarbodiimide (0.195 grams, 0.947 mmol), 1-hydroxybenzotriazole hydrate (0.116 grams, 0.861 mmol) and dimethyl formamide (5 mL) was stirred at ambient temperature until complete as determined by hplc (7 hours). The reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (4 x 25 mL). The organic extracts were combined, washed with saturated sodium chloride solution (2 x 35 mL), dried using sodium sulfate, and concentrated to an oil. The crude product was purified using preparative reverse phase hplc to give 0.32 grams (52%) of N-[(1R)-2-indol-3-yl-1-(N-{1-[2-(4-methyl piperidyl)-1-(2-naphthyl)-2-oxoethyl]imidazol-4-yl} carbamoyl)ethyl]-2-[(tert-butoxy)carbonylamino]-2-methylpropanamide. ^{1}H nmr ($CDCl_3$): 0.76-0.77 (d, 2H),

0.91-0.95 (m, 2H), 1.23-1.36 (m, 18H), 1.54 (m, 1H), 1.67 (m, 1H), 2.70-2.72 (m, 2H), 3.25-3.29 (m, 2H), 3.68 (m, 1H), 4.55-4.70 (m, 1H), 4.98 (m, 1H), 6.24 (m, 1H), 6.81-6.83 (d, 1H), 6.92 (m, 1H), 7.00-7.01 (m, 1H), 7.18-7.28 (m, 3H), 7.37-7.55 (m, 5H), 7.76-7.83 (m, 4H), 8.80 (s, broad, 1H), 10.38 (s, broad, 1H). ^{13}C nmr ($CDCl_3$): δ 14.60, 19.32, 19.47, 21.41, 21.83, 21.90, 25.39, 25.55, 26.04, 28.56, 28.63, 28.84, 31.05, 31.16, 31.21, 33.98, 34.08, 34.29, 34.69, 43.42, 46.28, 46.52, 49.38, 54.55, 56.99, 60.77, 62.31, 69.97, 71.02, 108.80, 110.24, 111.79, 119.02, 119.36, 121.86, 124.10, 125.99, 127.12, 127.36, 127.97, 128.08, 128.10, 128.16, 128.33, 128.63, 128.71, 129.77, 132.26, 133.63, 133.75, 134.02, 136.58, 137.29, 155.16, 157.65, 166.07, 166.18, 166.22, 166.34, 169.40, 171.52, 175.12.

Compound 64

N-[(1R)-2-Indol-3-yl-1-(N-{1-[2-(4-methylpiperidyl)-1-(2-naphthyl)-2-oxoethyl]imidazol-4-yl}carbamoyl)ethyl]-2-amino-2-methylpropanamide Dihydrochloride

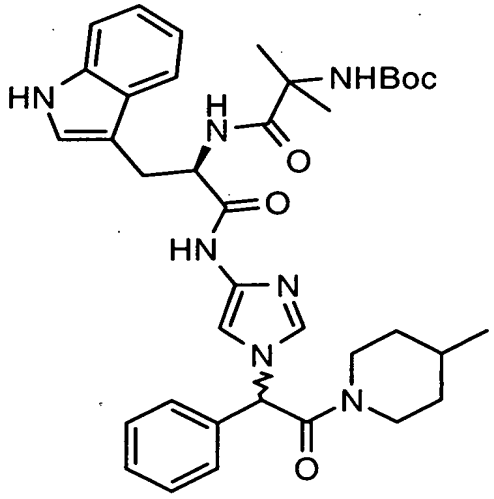


A solution consisting of N-[(1R)-2-indol-3-yl-1-(N-{1-[2-(4-methylpiperidyl)-1-(2-naphthyl)-2-oxoethyl]imidazol-4-yl}carbamoyl)ethyl]-2-[(tert-butoxy)carbonylamino]-2-methyl propanamide (0.32 grams, 0.445 mmol) and anisole (0.25 mL) dissolved in methylene chloride (20 mL) was added trifluoroacetic acid (2.5 mL). The resulting reaction mixture was stirred at ambient temperature until complete as determined by hplc (2.5 hours). The reaction mixture was concentrated to dryness. The residue was dissolved in methanol (5 mL) and applied to a Varian Mega Bond Elut SCX ion exchange column (5 gram). The column was washed with methanol (50 mL). The product was eluted from the column with 2N ammonia in methanol (30 mL). The eluent was concentrated to dryness to give the free base (0.28 grams). A 1.95 M solution of anhydrous HCl in ethyl acetate (0.456 mL, 0.89 mmol) was added to the free base which was dissolved in ethyl acetate (10 mL). The resulting precipitate was collected by filtration and dried in vacuum to give 0.27 grams (87%) of N-[(1R)-2-indol-3-yl-1-(N-{1-[2-(4-methylpiperidyl)-1-(2-naphthyl)-2-oxoethyl]imidazol-4-yl}carbamoyl)ethyl]-2-amino]-2-methylpropanamide dihydrochloride. MS (FIA) m/z 620.7 [$(M+H)^+$]. Anal. calcd. for $C_{36}H_{41}N_7O_3 \cdot 2HCl \cdot 1/2H_2O$: C: 61.62; H: 6.32; N: 13.97. Found: C: 61.42; H: 6.18; N: 13.62. Anal. calcd. exact mass for $C_{36}H_{42}N_7O_3$ [$(M+H)^+$] = 620.3349. Exact mass found by mass spectrometry: $C_{36}H_{42}N_7O_3$ [$(M+H)^+$] = 620.3355. ^1H nmr (DMSO-d_6): 0.65-0.67 (d, 2H), 0.89-0.90 (d, 2H), 1.16-1.24 (m, 2H), 1.35-1.36 (d, 4H), 1.51-1.53 (d, 4H), 1.63-1.65 (m, 1H), 2.68-2.74 (m, 1.5H), 3.08 (t, 0.5H), 3.17-3.19 (m, 1H), 3.26-3.27 (m, 1H), 3.71-3.82 (m, 1H), 4.40-4.55 (m, 1H), 4.71-4.72 (t, 1H), 6.90-7.00 (m, 1H), 7.02-7.04 (m, 1H), 7.26-7.33 (m, 3H), 7.52 (m, 1H), 7.59-7.62 (m, 3H), 7.74 (m, 1H), 7.98-8.09 (m, 4H), 8.31-8.32 (d,

3H), 8.49-8.61 (m, 1H), 8.66-8.68 (d, 1H), 10.94 (s, 1H), 11.35 (s, 1H).

Example 2-48

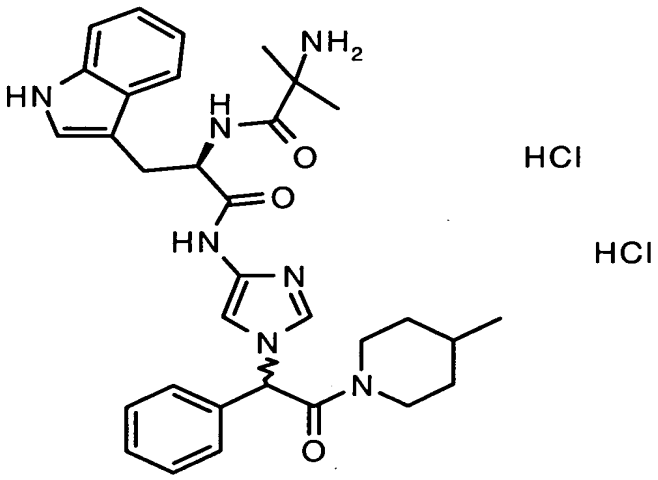
N-[(1R)-2-Indol-3-yl-1-(N-{1-[2-(4-methylpiperidyl)-2-oxo-1-phenylethyl]imidazol-4-yl}carbamoyl)ethyl]-2-[(tert-butoxy) carbonylamino]-2-methylpropanamide



This compound was obtained from the hydrolysis of ethyl 2-[4-((2R)-2-{2-[(tert-butoxy) carbonylamino]-2-methyl propanoylamino}-3-indol-3-ylpropanoylamino)imidazolyl]-2-phenylacetate and subsequent reaction with 4-methyl piperidine in 84% yield after Biotage Flash 40M purification using dichloromethane : methanol (24:1) as the eluent. MS (FIA) m/z 670.5 [$(M+H)^+$]. ^1H nmr ($CDCl_3$): δ 0.74-0.75 (d, 2H), 0.89-0.90 (d, 2H), 1.17-1.32(m, 18H), 1.53-1.63 (m, 3H), 2.66-2.70 (m, 1H), 3.05 (t, 1H), 3.15-3.20 (m, 1H), 3.69-3.83 (m, 1H), 4.36-4.49 (m, 1H), 4.67 (s, broad, 1H), 6.90-6.93 (m, 2H), 7.01-7.04 (m, 2H), 7.11 (s, 1H), 7.26-7.32 (m, 2H), 7.40-7.54 (m, 5H), 7.67 (s, broad, 1H), 8.16 (m, broad, 1H), 10.49 (s, broad, 1H), 10.84 (s, 1H).

Compound 65

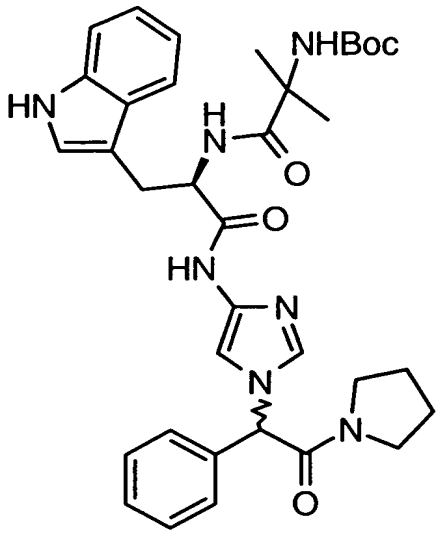
N-[(1R)-2-Indol-3-yl-1-(N-{1-[2-(4-methylpiperidyl)-2-oxo-1-phenylethyl]imidazol-4-yl}carbamoyl)ethyl]-2-amino-2-methyl propanamide Dihydrochloride



This compound was obtained from N-[(1R)-2-indol-3-yl-1-(N-{1-[2-(4-methylpiperidyl)-2-oxo-1-phenylethyl]imidazol-4-yl}carbamoyl)ethyl]-2-[(tert-butoxy)carbonylamino]-2-methyl propanamide as a red foam in 100% yield. MS (FIA) m/z 570.5 [$(M+H)^+$]. ^{1}H nmr (d-MeOH): δ 0.81-0.82 (d, 2H), 0.98-0.99 (d, 2H), 1.18-1.21 (m, 2H), 1.34-1.37 (m, 1H), 1.43 (s, 3H), 1.61 (s, 6H), 1.71 (t, 1H), 2.73-2.76 (m, 1.5H), 3.14 (t, 0.5H), 3.27-3.33 (m, 1H), 3.40-3.44 (m, 1H), 3.61-3.65 (m, 1H), 3.75-3.77 (d, 1H), 4.45-4.60 (m, 1H), 4.81 (s, broad, 4H), 6.94-6.99 (m, 1.5H), 7.06-7.07 (m, 1.5H), 7.19 (s, 1H), 7.31-7.35 (m, 2H), 7.52-7.61 (m, 6H), 8.62-8.65 (d, 1H).

Example 2-49

N-((1R)-2-Indol-3-yl-1-{N-[1-(2-oxo-1-phenyl-2-pyrrolidinylethyl)imidazol-4-yl]carbamoyl}ethyl)-2-[(tert-butoxy)carbonylamino]-2-methylpropanamide

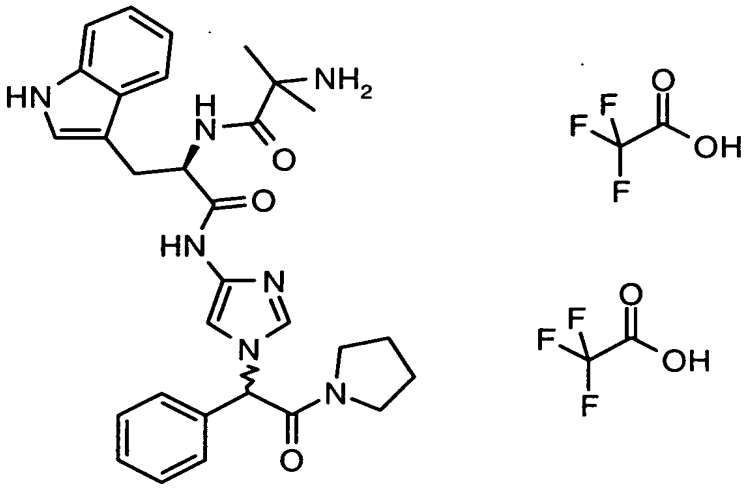


This compound was obtained from the hydrolysis of ethyl 2-[4-((2R)-2-{2-[(tert-butoxy) carbonylamino]-2-methyl propanoylamino}-3-indol-3-ylpropanoylamino)imidazolyl]-2-phenylacetate and subsequent reaction with pyrrolidine in 80% yield after purification by flash chromatography using dichloromethane : methanol (19:1) as the eluent. ^{1}H nmr ($CDCl_3$): δ 1.10-1.40 (m, 15H), 1.67-1.92 (m, 3H), 2.92-3.60 (m, 5H), 4.90 (s, broad, 1H), 5.33 (s, broad, 1H), 5.85 (d, 1H), 6.80-7.05 (m, 3H), 7.13-7.39 (m, 10H), 7.44-7.80 (m, 2H), 8.96 (s, broad, 1H), 10.20 (s, broad, 1H). ^{13}C nmr ($CDCl_3$): δ 14.25, 21.11, 24.02, 25.63, 26.08, 28.24, 33.87, 46.39, 46.64, 54.28, 56.67, 60.46, 63.07, 63.09, 108.33, 109.73, 110.69, 111.47, 118.36, 118.56, 119.05, 121.57, 123.77, 125.01, 126.42, 127.60, 128.51, 129.38,

133.14, 133.85, 136.23, 136.45, 136.49, 165.79, 165.85, 169.17, 174.87.

Compound 66

N-((1R)-2-Indol-3-yl-1-{N-[1-(2-oxo-1-phenyl-2-pyrrolidinyl ethyl)imidazol-4-yl]carbamoyl}ethyl)-2-amino-2-methyl propanamide Bistrifluoroacetic Acid

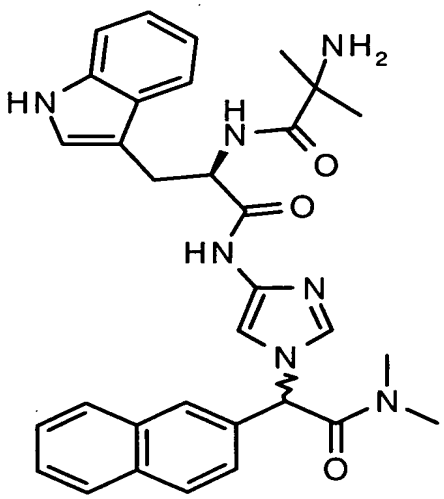


This compound was obtained from N-((1R)-2-indol-3-yl-1-{N-[1-(2-oxo-1-phenyl-2-pyrrolidinylethyl)imidazol-4-yl]carbamoyl}ethyl)-2-[(tert-butoxy)carbonylamino]-2-methylpropanamide as a white solid in 50% yield. MS (FD+) m/z 541 (M^+). Anal. calcd. for $C_{30}H_{35}N_7O_3 \cdot 2C_2HF_3O_2$: C: 53.06; H: 4.85; N: 12.74. Found: C: 52.93; H: 4.88; N: 12.55. ^1H nmr (DMSO-d_6): δ 1.29 (s, 3H), 1.46-1.48 (d, 3H), 1.72-1.88 (m, 4H), 2.94 (m, 1H), 3.06-3.07 (m, 1H), 3.19-3.20 (m, 1H), 3.40-3.41 (d, 2H), 3.67-3.69 (m, 1H), 4.78 (s, broad, 1H), 6.53 (s, 1H), 6.93-6.97 (m, 1H), 7.06 (m, 1H), 7.20 (d, 1H), 7.31-7.36 (m, 2H), 7.42-7.42 (m, 4H), 7.73-7.80 (m, 2H), 8.01 (s, broad, 2H), 8.36-8.38 (d, 1H), 10.82-10.85 (d, 2H).

Example 2-50

Compound 67

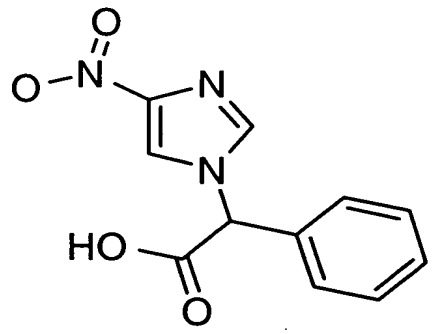
N-[(1R)-1-(N-{1-[(N,N-Dimethylcarbamoyl)-2-naphthylmethyl}imidazol-4-yl}carbamoyl)-2-indol-3-ylethyl]-2-amino-2-methyl propanamide Dihydrochloride



This compound was obtained from the reaction of 2-[4-((2R)-2-{2-[(tert-butoxy)carbonylamino]-2-methylpropanoylamino}-3-indol-3-ylpropanoylamino) imidazolyl]-2-(2-naphthyl)acetic acid and dimethylamine followed by deprotection according to the general procedure as an off white solid in 90% yield. MS (FIA) m/z 566.6 [$(M+H)^+$]. ^{1}H nmr (DMSO-d_6): δ 1.36-1.37 (d, 3H), 1.51-1.53 (d, 3H), 2.92 (s, 3H), 2.99 (s, 3H), 3.19-3.22 (m, 1H), 3.27-3.31 (m, 1H), 4.68-4.73 (m, 1H), 6.90-6.94 (m, 1H), 6.97-7.03 (m, 1H), 7.29-7.33 (m, 2H), 7.38 (s, 1H), 7.55 (s, 1H), 7.60-7.62 (t, 3H), 7.73 (t, 1H), 7.98-8.06 (m, 4H), 8.36-8.37 (d, 3H), 8.72-8.74 (d, 2H), 10.97 (s, 1H), 11.49 (s, 1H).

Example 2-51

2-(4-Nitroimidazolyl)-2-phenylacetic acid

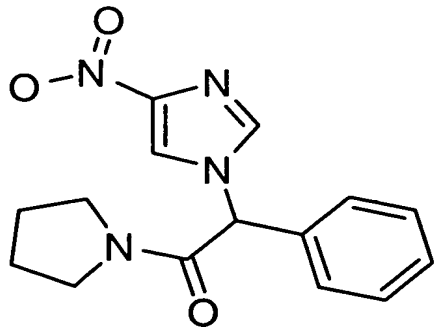


1

Lithium hydroxide (18.1 g, 750 mm, 2 eq) was added to a stirred slurry of ethyl 2-(4-nitroimidazoyl)-2-phenylacetate (104 g, 379 mm) in 250 mL of ethanol. Deionized water was added to the resulting mixture and the stirring was continued for 4 hours. The ethanol was removed under vacuum and the resulting aqueous solution was washed with 100 mL of diethyl ether. The aqueous layer was diluted with 100 mL of deionized water and the pH was adjusted to 1.8 with concentrated HCl after cooling to 12 ^{0}C. The resulting slurry was stirred for 30 minutes at less than 5 degrees and filtered. The wet cake was washed with 100 mL of deionized water and dried under a stream of air on the filter overnight to yield 90.34 g (96%) of a brown solid. The product may be recrystallized from isopropyl alcohol to give 72.31 g (80% recovery, 77% overall yield) of a tan solid. Elemental analysis: Calculated: %C 53.45, %H 3.67, %N 16.97; Found: : %C 53.67, %H 3.79, %N 16.65. MS: 247 (M^{+}): IR (cm^{-}

^{1})1719; H^1 nmr (d^6 DMSO): d 6.51 (s, 1H), 7.43-7.55 (m,5H), 7.95 (s,1H), 8.40 (s, 1H)

2-(4-Nitroimidazolyl)-2-phenyl-1-pyrrolidinylethane-1-one

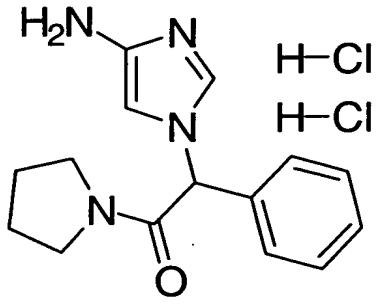


3

N-Methyl morpholine (22.25 ml, 2 eq) was added to a stirred solution of 2-(4-nitroimidazolyl)-2-phenylacetic acid (**1**) (25.03 g, 101.2 mm) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (18.1 g, 101.2 mm, 1.0 eq) in 50 ml of anhydrous tetrahydrofuran at 25^0 C. After stirring the reaction mixture at ambient temperature for 1 h, 7.2 mL (101.2 mm, 1.0 eq) of pyrrolidine was added dropwise. The reaction was stirred at room temperature for 2 hours. The reaction mixture was quenched by the addition of 200 mL of ethyl acetate and 200 mL of 1M HCl. The layers were separated and the organic layer was washed with 100 mL of saturated sodium bicarbonate solution. The mixture resulting from the bicarbonate wash was diluted 1:1 with deionized water to dissolve the resulting solids and the layers were separated. The organic layer was washed with brine, dried over magnesium sulfate, filtered and the volatiles were removed under vacuum to give a brown foam. This foam was dissolved in methanol,

diethyl ether and methylene chloride. Evaporation of the solvents overnight yielded a brown solid which was slurried in 200 mL of diethyl ether for 4 hours. The resulting slurry was filtered and the cake was washed with diethyl ether. The solids were dried under vacuum overnight to give a cream colored product (21.68 g, 71%) d (d^6 DMSO):1.69-1.84 (m, 3H), 2.80-2.85 (m, 0.7H), 3.32 - 3.41 (m, 3.6H), 3.64-3.67 (m, 0.7H), 6.65 (s, 1H), 7.42-7.50 (m, 5H), 7.83 (s, 1H), 8.22 (s, 1H)

2-(4-aminoimidazolyl)-2-phenyl-1-pyrrolidinylethan-1-one, dihydrochloride

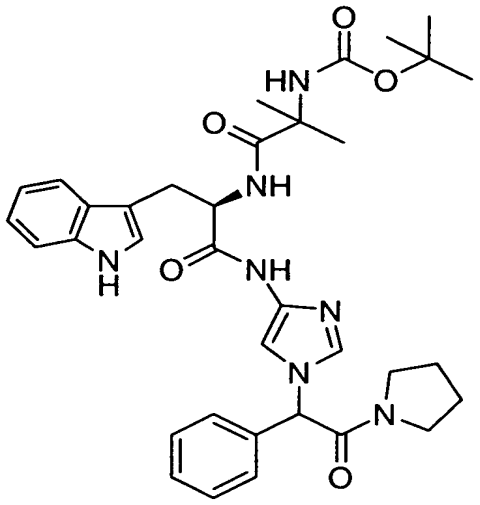


6

Ethanol (200 mL) was added to a mixture of 2-(4-nitroimidazolyl)-2-phenyl-1-pyrrolidinylethan-1-one (**3**) (0.752 g, 2.8 mm) and 10% Pd on carbon (75 mg) in a Bradley hydrogenation apparatus. The stirred reaction mixture was subjected to a 60 psi H_2 atmosphere and warmed to 60 ^{0}C. After 2 hours, the reaction mixture was cooled to room temperature and the catalyst was removed by filtration. Anhydrous HCl gas was added to the filtered solution until saturation. The volatiles were then removed under vacuum to give a light yellow foam. Diethyl ether and methylene chloride (25:1) were added to

the foam and the resulting mixture was stirred overnight to achieve crystallization. The resulting slurry was filtered and the cake was washed with diethyl ether. The cake was dried under vacuum to give 0.659 g (93%) of a yellow solid. LGD 208.

N-((1R)-2-indol-3-yl-1-{N-[1-(2-oxo-1-phenyl-2-pyrrolidinylethyl)imidazol-4-yl]carbamoyl}ethyl)-2-[(tert-butoxy)carbonylamino]-2-methylpropanamide



8

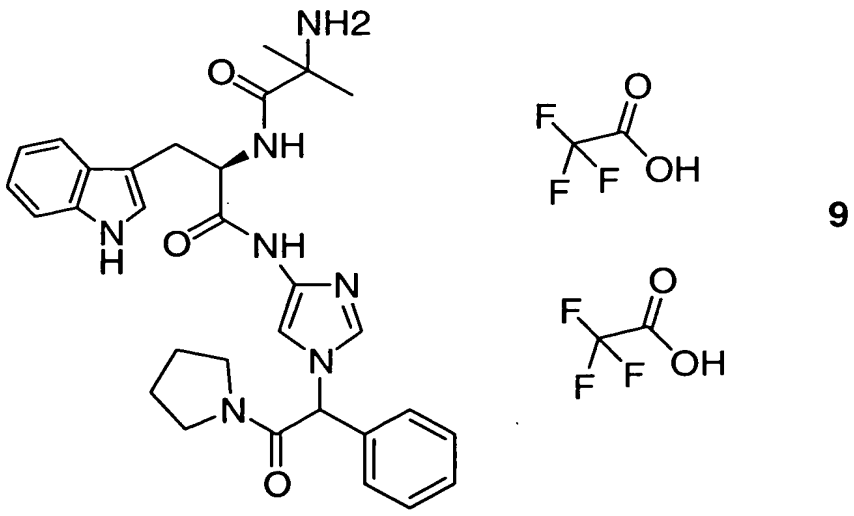
N-Methyl morpholine (0.28 mL, 8.32 mm, 1 eq) was added to a stirred slurry of 2-chloro-4,6-dimethoxy-1,3,5-triazine (0.46 g, 2.57 mm, 1 eq) and (2R)-2-{2-[(tert-butoxy)carbonylamino]-2-methylpropanoylamino}-3-indol-3-ylpropanoic acid (1g, 2.57mm) in 10 mL of anhydrous tetrahydrofuran cooled to less than 0 ^{0}C. After 1.5 hours, 2-(4-aminoimidazolyl)-2-phenyl-1-pyrrolidinylethan-1-one, hydrochloride (0.97g, 2.82 mm, 1.1 eq) was added and stirring was continued at ice bath temperatures. The reaction was stirred for 4 hours and quenched by

the addition of 15 mL of deionized water and ethyl acetate. The ethyl acetate layer was washed with a saturated sodium bicarbonate solution, dried over magnesium sulfate and the volatiles were removed under vacuum to give the crude product as a light purple foam (1.4 g, 84%) The crude product was purified by preparative chromatography to provide 0.52 g (31.5%) of the product as a foam. ^{1}H nmr ($CDCl_3$): δ 1.10-1.40 (m, 15H), 1.67-1.92 (m, 3H), 2.92-3.60 (m, %H), 4.90 (s, broad, 1H), 5.33 (s, broad, 1H), 5.85 (d, 1H), 6.80-7.05 (m, 3H), 7.13-7.39 (m, 10H), 7.44-7.80 (m, 2H), 8.96 (s, broad, 1H), 10.20 (s, broad, 1H).

Example 2-52

Compound 68

***N*-((1R)-2-indol-3-yl-1-{N-[1-(2-oxo-1-phenyl-2-pyrrolidinylethyl)imidazol-4-yl]carbamoyl}ethyl)-2-amino-2-methylpropanamide, 2,2,2-trifluoroacetic acid, 2,2,2-trifluoroacetic acid salt**



9

Trifluoroacetic acid (0.57 mL, 7.4 mm, 33 eq) was added to a stirred solution of *N*-((1R)-2-indol-3-yl-1-{N-[1-(2-oxo-1-phenyl-2-pyrrolidinylethyl)-imidazol-4-yl]carbamoyl}ethyl)-2-[(tert-butoxy)-carbonylamino]-2-methylpropanamide **(8)** (0.152 g, 0.22 mm) in 5 mL of methylene chloride. After stirring at room temperature for 3 hours, the reaction mixture was diluted with 50 mL of diethyl ether. The resulting solids were isolated by centrifugation and washed with diethyl ether. The solids were dried under vacuum to give the product as a cream colored solid (0.084 g, 48%) MS (FD+) m/z 541 (M^+)Anal. calcd. for $C_{30}H_{35}N_7O_3 \cdot 2C_2HF_3O_2$: C: 53.06; H: 4.85; N: 12.74. Found: C: 52.93; H: 4.88; N: 12.55. ^1H nmr (DMSO-d_6): δ 1.29 (s, 3H), 1.46-1.48 (d, 3H), 1.72-1.88 (m, 4H), 2.94 (m, 1H), 3.06-3.07 (m, 1H), 3.19-3.20 (m, 1H), 3.40-3.41 (d, 2H), 3.67-3.69 (m, 1H), 4.78 (s, broad, 1H), 6.53 (s, 1H), 6.93-6.97 (m, 1H), 7.06 (m, 1H), 7.20 (d, 1H), 7.31-7.36 (m, 2H), 7.42-7.42 (m, 4H), 7.73-7.80 (m, 2H), 8.01 (s, broad, 2H), 8.36-8.38 (d, 1H), 10.82-10.85 (d, 2H).

Example 2-53

Additional Compounds

Additional compounds of Formula I were also synthesizes my methods similar to the foregoing. These compounds included those wherein:

a) R1 is $C_6H_5(CH_2)_3$-, R3 is phenyl, R4 is H, and Y is pyrrolidin-1-yl,

b) R1 is $C_6H_5CH_2OCH_2$-, R3 is phenyl para-substituted by W, W is phenyl, R4 is H, and Y is pyrrolidin-1-yl,

c) R1 is indol-3-ylmethyl, R3 is phenyl para-substituted by W, W is phenyl, R4 is H, and Y is pyrrolidin-1-yl,

d) R1 is indol-3-ylmethyl, R3 is phenyl para-substituted by W, W is $-OCH_3$, R4 is H, and Y is pyrrolidin-1-yl,

e) R1 is $C_6H_5(CH_2)_3-$, R3 is phenyl para-substituted by W, W is CF_3, R4 is H, and Y is 4-methylpiperidin-1-yl,

f) R1 is $C_6H_5(CH_2)_3-$, R3 is phenyl para substituted by W, W is phenyl, R4 is H, and Y is pyrrolidin-1-yl,

g) R1 is $C_6H_5(CH_2)_3-$, R3 is phenyl para substituted by W, W is F, R4 is methyl, and Y is pyrrolidin-1-yl,

h) R1 is $C_6H_5CH_2OCH_2-$, R3 is phenyl para substituted by W, W is F, R4 is methyl, and Y is pyrrolidin-1-yl,

i) R1 is $C_6H_5(CH_2)_3-$, R3 is phenyl para substituted by W, W is F, R4 is methyl, and Y is 4-methylpiperidin-1-yl,

j) R1 is $C_6H_5(CH_2)_3-$, R3 is 2-naphthyl, R4 is methyl, and Y is 4-methylpiperidin-1-yl,

k) R1 is $C_6H_5CH_2OCH_2-$, R3 is 2-naphthyl, R4 is methyl, and Y is 4-methylpiperidin-1-yl,

l) R1 is $C_6H_5(CH_2)_3-$, R3 is phenyl para-substituted by W, W is CF_3, R4 is methyl, and Y is 4-methylpiperidin-1-yl, and

m) R1 is $C_6H_5CH_2OCH_2-$, R3 is phenyl, R4 is H, and Y is 4-methylpiperidin-1-yl

Example 3

Pituitary Cell Culture Assay for Growth Hormone Secretion

Thirty-two 250 g male Sprague-Dawley rats were used for each assay. The animals were killed by decapitation and anterior pituitaries were removed and placed into ice cold culture medium. The pituitaries were sectioned into eighths and enzymatically digested using trypsin (Sigma Chemical) to weaken connective tissue. Pituitary cells were dispersed by mechanical agitation, collected, pooled and then seeded into 24-well plates (300,000 cells/well). After 4 days of culture, the cells formed an even monolayer. Cells were then washed with medium and challenged to secrete GH by the addition of GH secretagogues to the medium. After 15 min at

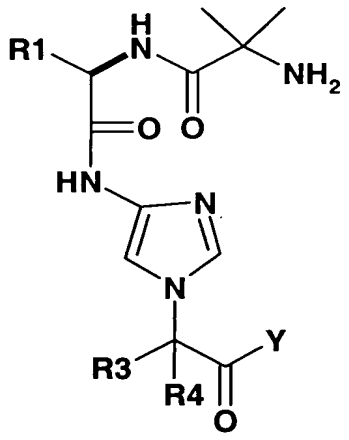
37 °C, the medium was removed and stored frozen until radioimmunoassays for rat GH were performed. Doses of secretagogue were added in quadruplicate. Representative data is provided in Table 1 below. Compounds disclosed herein are active in the assay as described. Both EC_{50} and efficacy values were calculated by the 4-parameter logistic equation. Such values were pooled and represented as mean +/- standard error, when appropriate.

Table 1

EXAMPLES PART 1 Example #	GH secretion EC_{50} (μM)
6	5.53
8	2.39

We claim:

1. A compound of Formula I



wherein:
R^1 is $C_6H_5CH_2OCH_2$-, $C_6H_5(CH_2)_3$- or indol-3-ylmethyl;
Y is pyrrodidinyl, 4-methyl piperidinyl or NR2R2;
R2 are each independently a C_1 to C_6 alkyl;
R3 is 2-napthyl or phenyl para-substituted by W;
W is H, F, CF_3, C_1-C_6 alkoxy or phenyl; and
R4 is H or CH_3,
or a pharmaceutically salt or solvate thereof.

2. A compound of Claim 1 wherein R^4 is CH_3.

3. A compound of Claim 1 wherein said compound has the (R,R) stereo configuration.

4. A method for increasing the level of endogenous growth hormone in a human or an animal which comprises administering to said human or animal an effective amount of a compound of Claim 1.

5. A method for the treatment or prevention of a physiological condition which may be modulated by an increase in endogenous growth hormone which comprises

administering to an animal in need of said treatment an effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt or solvate thereof.

6. A pharmaceutical formulation which comprises, as an active ingredient a compound of Claim 1, or a pharmaceutically acceptable salt or solvate thereof, associated with one or more pharmaceutically acceptable carriers, diluents, or excipients.

7. A pharmaceutical formulation according to Claim 6 which further comprises a bone-antiresorptive agent.

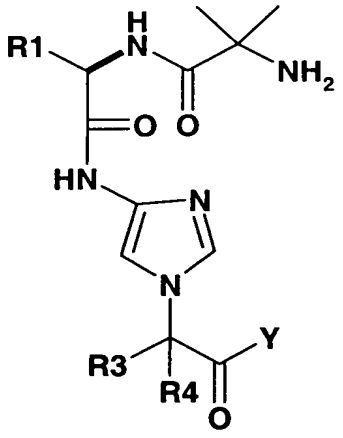
8. A method according to Claim 7 which further comprises administering to a patient a bone antiresorptive agent.

9. A method according to Claim 8 wherein said bone antiresorptive agent is a bisphosphonate.

Abstract of the Disclosure

Growth Hormone Secretagogues

What is disclosed are growth hormone secretagogues, and their uses, of the formula



wherein R1 is $C_6H_5CH_2OCH_2$-, $C_6H_5(CH_2)_3$- or indol-3-ylmethyl; Y is pyrrolidin-1-yl, 4-C_1-C_6 alkylpiperidin-1-yl or NR2R2; R2 are each independently a C_1 to C_6 alkyl; R3 is 2-napthyl or phenyl para-substituted by W; W is H, F, CF_3, C_1-C_6 alkoxy or phenyl; and R4 is H or CH_3,

or a pharmaceutically acceptable salt or solvate thereof.